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Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Research policies, see Authors & Referees and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒ A description of all covariates tested
☐	☒ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	Western blot images were captured by Amersham Imager 680 and its Analysis Software. ImageJ 1.51j8 was used for protein quantification. Image Pro 9.1 was used for quantification of atherosclerotic plaque size. qRT-PCR data were collected using a 7500 Real Time PCR machine (Applied Biosystems) and its software v2.3.
Data analysis	GraphPad Prism 8.4.2 was used for statistical analysis. Qlucore Omics Explorer 3.5 was used for compiling heatmap.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors/reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

The data that support the findings of this study are available from the corresponding author upon request. Source data for Figs. 1-7 and Extended Data 1-10 are provided online linked to this article. The RNA-Seq data have been deposited in the GEO repository (accession # GSE148301). The genes regulated by ATF3 are presented in Supplementary Data 1.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Sample size was based on statistical analysis of variance and on our prior experience with similar in vitro or in vivo studies (PubMed: 31604677, 31291759).
Data exclusions	No data were excluded.
Replication	All the studies except for the atherosclerosis studies were repeated once with similar results. The studies on the role of ATF3 in atherosclerosis was not repeated but each study was carried out independently. Importantly, all the conclusions were also supported by alternative approaches.
Randomization	Randomization was done manually without knowing which cells, mice or humans would be assigned as treatment or control groups.
Blinding	The person who performed studies on atherosclerosis or staining was blinded to group allocation. For most other studies, investigators were not blinded to group allocation, but they were not informed of expected treatment results before or during experimentation.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☐	☒ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology
☐	☒ Animals and other organisms
☐	☒ Human research participants
☒	☐ Clinical data

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used	The following antibodies were used: ApoB: Meridian Life Science, cat # K45253G. ApoE: Novus Biologicals, cat # NB110-60531. Lot # D-2. ATF3: Novus Biologicals, cat # NBP1-85816. Lot # 000006139. ATF3: Abcam, cat # ab207434. Lot # GR3204423-1. Calnexin: Novus Biologicals, cat # NB100-1965. CYP7A1: Origene Technologies, cat # TA351400. Lot # Y1909A141028. CYP8B1: Origene Technologies, cat # TA313734. Lot # 20110119007. FLAG: Sigma, cat # F1804. LDLR: Novus Biologicals, cat # NBP1-06709. Lot # C-2. MOMA2: Bio-Rad, Cat # MCA519G. MTP: Santa Cruz Biotechnology, cat # sc-135994. P53: Santa Cruz Biotechnology, cat # sc-6243. Lot # A1012 SR-BI: Novus Biologicals, cat # NB400-101. Lot # L. Tubulin: Abcam, cat # ab4074. Lot # GR3354062-3.
Validation	All the antibodies were commercially available and their validation statements are available on the manufacturers' websites. All antibodies were validated as per manufacturers' instructions. We also used tissues collected from knockout mice to validate ATF3, p53, SR-BI, ApoE, and LDLR antibodies, and tissues collected from over-expression studies to validate CYP7A1, CYP8B1 and ATF3 antibodies.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	HepG2 cells were purchased from the American Type Culture Collection (ATCC, Rockville, MD, USA).
Authentication	HepG2 cells were purchased directly from ATCC, and have been authenticated by ATCC. We did not further authenticate HepG2 cells.
Mycoplasma contamination	HepG2 cells were tested negative for mycoplasma by PCR.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used.

Animals and other organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research

Laboratory animals	Mice were used with mean age of 10 weeks plus/minus 2 weeks. They were on a C57BL/6 background. Only male mice were used in the studies.
Wild animals	The study did not involve wild animals.
Field-collected samples	No field collected samples were used in the study.
Ethics oversight	All the mouse studies were approved by the Institutional Animal Care and Use Committee at Northeast Ohio Medical University and were in accordance with NIH guidelines for the care and use of laboratory animals.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Human research participants

Policy information about studies involving human research participants

Population characteristics	The population characteristics is provided in Supplementary Table 1.
Recruitment	The participants were patients and were not recruited for the purpose of this study. Human liver tissues and paired plasma were collected at the Union Hospital of Tongji Medical College in Huazhong University of Science and Technology. There was no self-selection or other bias.
Ethics oversight	All the studies were approved by the Institutional Review Board (IRB) at Northeast Ohio Medical University (for using human primary hepatocytes) or the Union Hospital of Tongji Medical College in Huazhong University of Science and Technology (for collecting human tissues). Informed consent was obtained from human participants and the collection of human tissues was approved by the IRB at the Union Hospital of Tongji Medical College in Huazhong University of Science and Technology.

Note that full information on the approval of the study protocol must also be provided in the manuscript.